Effect of systemic N-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans

S. ILLKJAER, K. L. PETERSEN, J. BRENNUM, M. WERNBERG AND J. B. DAHL

Summary

Ketamine reduces nociception by binding non-competitively to the N-methyl-D-aspartate (NMDA) receptor, activation of which increases spinal hypersensitivity. We studied 19 healthy, unmedicated male volunteers, aged 20–31 yr. Burn injuries were produced on the medial surface of the dominant calf with a 25 × 50 mm rectangular template. On 3 separate days, at least 1 week apart, subjects received a bolus of either ketamine 0.15 mg kg⁻¹, ketamine 0.30 mg kg⁻¹ or placebo, delivered by a mechanical infusion pump over 15 min. The bolus was followed by continuous infusion of ketamine 0.15 mg kg⁻¹ h⁻¹, ketamine 0.30 mg kg⁻¹ h⁻¹ or placebo, respectively, for 135 min. Ketamine reduced the magnitude of both primary and secondary hyperalgesia, and also pain evoked by prolonged noxious heat stimulation, in a dose-dependent manner. In contrast, ketamine did not alter phasic heat pain perception (perception of transient, painful, thermal stimuli) in undamaged skin. The analgesic effects of ketamine in the burn injury model are in agreement with results from experimental studies, and can be distinguished from those of local anaesthetics and opioids. Side effects caused by continuous infusion of ketamine 0.15 and 0.30 mg kg⁻¹ h⁻¹ were frequent but clinically acceptable. (Br. J. Anaesth. 1996; 76: 829–834)

Key words


Peripheral tissue damage results in sensitization of dorsal horn neurones. One consequence is altered processing of afferent activity evoked by innocuous in addition to noxious stimuli, which is manifested clinically as allodynia (pain caused by a stimulus that does not normally provoke pain) and hyperalgesia (increased response to a stimulus that is normally painful) [1]. Injury-induced sensitization of dorsal horn neurones has been implicated as an important contributor to both acute and some chronic pain states [2]. In recent years the role of excitatory amino acids in nociception has been highlighted [3]. Glutamate and aspartate participate in the activation of nociceptive dorsal horn neurones as agonists for the N-methyl-D-aspartate (NMDA) receptor. There is substantial evidence that this receptor plays a significant role in spinal hypersensitivity, leading to renewed interest in NMDA receptor antagonists such as ketamine [3].

Ketamine has been used as an anaesthetic-antalgic agent for more than 30 yr. Its mechanism of action has been disputed [4] but it is now generally agreed that one pharmacological mechanism of the antinociceptive action is specific binding to the phencyclidine (PCP) site of the NMDA receptor-gated ion channel. This results in non-competitive, use-dependent NMDA receptor antagonism [5]. In experimental studies ketamine reduced NMDA-mediated nociceptive responses in dorsal horn neurones [6]. Clinical studies with ketamine indicated a role for NMDA receptors in acute postoperative [7–10], and also chronic neuropathic pain [11, 12].

A cutaneous heat injury evokes hyperalgesia for mechanical and heat stimuli within the injured area (primary hyperalgesia) and hyperalgesia for mechanical, but not heat, stimuli in an area surrounding the injury (secondary hyperalgesia) [13]. There is convincing evidence that secondary hyperalgesia is a result of altered central processing of afferent input because of sensitization of dorsal horn neurones, whereas primary hyperalgesia seems to be caused by a combination of sensitization of peripheral receptors and central neurones [14–18]. The burn injury model has been used previously to study the effects of various analgesics in human volunteers [19, 20].

The aim of this study was to investigate the effects of systemic ketamine, in clinically relevant analgesic doses, on pain and hyperalgesia after a burn injury in human volunteers.

Subjects and methods

We studied 19 healthy, unmedicated male volunteers, aged 20–31 yr, after obtaining informed consent and approval from the regional Ethics Committee and the Danish National Health Board. The study was performed in a quiet room with the subjects in a semi-supine position. Each subject had been familiarized with the burn injury and measurement procedures on a separate day.

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HYPERALGESIA

Burn injuries were produced on the medical surface of the dominant calf (L3–4 dermatome), with a 25 × 50 mm rectangular thermode (Thermotest, Somedic AB, Sweden), applied to the skin with a standardized pressure (8 kPa). The temperature of the thermode was 47 °C, and the application time was 7 min. This resulted in a first-degree burn injury, that is redness without blistering.

Pain ratings were performed continuously by the volunteer during the burn injury with an electronic visual analogue scale (VAS). The VAS was anchored with the descriptors “no pain” and “worst possible pain”. Pain ratings were sampled at a rate of 2 Hz. The interpretation of “pain” was left to the subject, who was instructed to apply the same interpretation throughout the study.

Brief conditioning (“priming” of the central nervous system with afferent input in C-fibres) was produced with the same thermode placed on the centre of the anterior side of the thigh at 45 °C. After 3 min of heating, the border of hyperalgesia to punctuate stimuli was determined along four linear paths arranged radially around the thermal injury (see below). Immediately after these determinations the thermode was removed. These brief conditioning stimuli induced slight or no pain during heating and no spontaneous sensations after termination. The mechanical hyperalgesia induced by these brief conditioning stimuli never lasted more than a few minutes beyond the duration of the conditioning stimuli.

MEASUREMENT OF THERMAL THRESHOLDS

Thermal thresholds were measured with a computerized Thermotest (Somedic AB, Sweden). Heat pain detection threshold (HPDT) was defined as the lowest temperature perceived as painful. The thermode was identical to that used for production of the burn injury.

HPDT was determined from a baseline temperature of 32 °C with a rate of change of 1 °C s⁻¹. By pressing a button, subjects indicated when the pertinent threshold was reached. This value was recorded, and the stimulator returned to baseline. If the cut-off limit (52 °C) was reached before the pertinent threshold, the thermode automatically returned to baseline and a threshold of 52 °C was registered (this was the case in three of 570 threshold determinations). Each threshold was calculated as the average of three measurements with intervals of 10 s between each stimulation. Thermal thresholds were determined at the site of injury and at the corresponding site of the contralateral, unburned calf.

MEASUREMENT OF MECHANICAL HYPERALGESIA

The temperature of the injured site was stabilized at 36 °C, with the above described thermode, from 5 min before and throughout assessments of mechanical hyperalgesia. The border of hyperalgesia to punctuate and stroke stimuli was determined by stimulating along four linear paths arranged radially around the thermal injury in steps of 5 mm at intervals of 1 s, starting well outside the hyperalgesic area where neither stimulus type evoked pain. The stimulations continued towards the injury until subjects reported a clear change in sensation (“burning”, “tenderness”, “more intense pricking”). The areas of hyperalgesia were calculated using a vector algorithm [19]. Punctuate stimulation was performed with the von Frey technique using a nylon filament with a diameter of 1 mm and a bending force of 1.15 N. Stroke stimulation was performed by lightly stroking the skin with a gauze swab.

ASSESSMENT OF SIDE EFFECTS

Drowsiness was assessed on an 11-point analogue scale (0 = completely awake; 10 = almost asleep). Discomfort was assessed on an 11-point analogue scale (0 = no discomfort; 10 = maximum discomfort). Hallucinations (yes/no) were registered after bolus injection. Finally, subjects were asked if they experienced other sensations (Table 1).

EXPERIMENTAL PROCEDURE

On 3 separate days, at least 1 week apart, subjects received a bolus of either ketamine 0.15 mg kg⁻¹, ketamine 0.30 mg kg⁻¹ or placebo, delivered by a mechanical infusion pump over 15 min. The bolus dose was followed by a continuous infusion of ketamine 0.15 mg kg⁻¹ h⁻¹, ketamine 0.30 mg kg⁻¹ h⁻¹ or placebo, respectively, for 135 min. The time to

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<td>0–15 min</td>
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administer the bolus injection and doses of ketamine were chosen on the basis of a small pilot study, performed in order to determine doses with acceptable side effects. The study was double-blind, and the order of treatments was randomized. The time course of the various assessments are shown in table 1.

**STATISTICAL ANALYSIS**

Data are presented as median (range). Variables were evaluated with non-parametric two-way analysis of variance for repeated measurements, Friedmann’s analysis of variance and Wilcoxon’s test for paired data, where appropriate. \( P \leq 0.05 \) was considered statistically significant.

**Results**

**CONTROL (PLACEBO) DAY**

Pain during burn injury increased rapidly during the first 15–30 s, reached a plateau and then remained relatively stable during the remaining 6 min (fig. 1). After injury, no spontaneous pain or other sensations were experienced from the site of injury.

HPDT inside the burn injury decreased from a baseline value of 45.9 (44.6–47.6) °C to 41.6 (39.0–44.8) °C, 100 min after the injury (Friedmann’s ANOVA, \( P < 0.0001 \)), and remained decreased throughout the study (fig. 2).

HPDT on the contralateral calf did not change during the study (fig. 2). The borders of secondary hyperalgesia for punctuate and stroke stimuli (fig. 3) surrounding the burn injury on the calf and the area of secondary hyperalgesia for punctuate stimuli evoked by brief conditioning on the thigh (fig. 4) were detected easily in all subjects.

**EFFECTS OF KETAMINE**

Pain during burn injury was reduced in a dose-dependent manner by ketamine (fig. 1). The initial rapid increase in pain observed during placebo treatment was diminished, and the plateau level was reduced (low-dose \( v \) placebo, \( P < 0.07 \); high-dose \( v \) placebo, \( P < 0.007 \); Wilcoxon rank test).

At the site of injury there was no difference in the decrease in HPDT between placebo and low-dose ketamine treatments (\( P > 0.7 \); two-way ANOVA), whereas HPDT was reduced less during high-dose ketamine compared with placebo after injury (\( P < 0.03 \); two-way ANOVA). Hence, high-dose ketamine diminished primary hyperalgesia (fig. 2).

At the contralateral uninjured calf there was no difference in HPDT either between low-dose ketamine and placebo or between high-dose ketamine and placebo (\( P = 0.43 \) and \( P = 0.07 \), respectively; two-way ANOVA) (fig. 2).

The areas of secondary hyperalgesia for punctuate and stroke stimuli were both reduced by high-dose ketamine compared with placebo (\( P < 0.004 \) and

![Figure 1](image1.png) Pain (VAS) during burn injury during infusion of placebo (---), ketamine 0.15 mg kg\(^{-1}\) (-----) or ketamine 0.30 mg kg\(^{-1}\) (---) (medians). The initial rapid increase in pain observed during placebo treatment (top) was diminished, and the plateau level was reduced (bottom) (ketamine 0.15 mg kg\(^{-1}\) \( v \) placebo: \( P < 0.07 \); ketamine 0.30 mg kg\(^{-1}\) \( v \) placebo: \( P < 0.007 \), Wilcoxon rank test).

![Figure 2](image2.png) Heat pain detection threshold (HPDT) on the unburned (top) and burned (bottom) calf (medians) before (baseline (B) and before the burn injury (Pre)) during and after infusion of placebo (○), ketamine 0.15 mg kg\(^{-1}\) (△) or ketamine 0.30 mg kg\(^{-1}\) (□). Start, stop = Beginning and end of infusion of ketamine or placebo. Ketamine 0.15 mg kg\(^{-1}\) \( v \) placebo: \( P > 0.05 \); ketamine 0.30 mg kg\(^{-1}\) \( v \) placebo: \( P > 0.05 \), non-parametric two-way analysis for unburned calf; ketamine 0.15 mg kg\(^{-1}\) \( v \) placebo: \( P > 0.05 \); ketamine 0.30 mg kg\(^{-1}\) \( v \) placebo; \( P < 0.05 \), non-parametric two-way analysis for burned calf. Filled symbols = significant difference from baseline (Friedman’s ANOVA).
P < 0.002, respectively; two-way ANOVA) (fig. 3). Low-dose ketamine only reduced the area of secondary hyperalgesia for stroke (P = 0.03; two-way ANOVA) (fig. 3).

Both low- and high-dose ketamine reduced the area of secondary hyperalgesia for punctuate stimuli evoked by brief conditioning on the thigh (P < 0.05 and P < 0.03, respectively; two-way ANOVA) (fig. 4).

SIDE EFFECTS

Ketamine induced drowsiness in all volunteers in a dose-dependent manner (fig. 5). Varying degrees of drowsiness (range 1–6 on the analogue scale), however, were also experienced by three volunteers during placebo treatment. Two volunteers experienced some degree of discomfort (range 1–6 on the analogue scale) after bolus injection of ketamine 0.15 mg kg\(^{-1}\) compared with five subjects after bolus injection of ketamine 0.30 mg kg\(^{-1}\) compared with five subjects after bolus injection of ketamine 0.30 mg kg\(^{-1}\).

Discussion

Experimental studies have demonstrated that dorsal horn neurones may display an altered response to both nociceptive and non-nociceptive afferent input after peripheral tissue damage or intense electrical C-fibre stimulation. These alterations include facilitation of the flexor motorneuronal responses, expansion of receptive fields and a decrease in the activation threshold of dorsal horn neurones [1, 2]. The mechanisms of these alterations include induction of wind-up, whereby responses of dorsal horn neurones increase during repetitive constant intensity C-fibre stimuli, that is increased duration.
Ketamine and hyperalgesia

and magnitude of the cell responses [21]. There is substantial evidence that the NMDA receptor plays a significant role in wind-up and spinal hypersensitivity [1–3].

The mechanism of action of NMDA receptor antagonists differs from that of "classical" analgesics such as opioids. Opioids most probably reduce C-fibre input to the dorsal horn nociceptive neurones and consequently delay the onset and reduce the magnitude of wind-up and spinal hypersensitivity [22]. In contrast, the NMDA receptor antagonist ketamine has no effect on the initial input, but reduces wind-up [23]. Two recent studies in human volunteers confirmed these experimental observations [24, 25]. In one study, the NMDA receptor antagonist dextromethorphan reduced temporal summation of second pain, a psychophysical correlate of wind-up, whereas neither first nor second pain evoked by a single stimulus was affected by the drug [24]. In the other study, high-dose ketamine (bolus 0.5 mg kg\(^{-1}\), followed by a 20-min infusion of 0.54 mg kg\(^{-1}\) h\(^{-1}\)) reduced central temporal summation to repeated noxious electrical stimuli, whereas reflex and pain ratings to a single stimulus were unaltered [25]. The high dose of ketamine used in the latter study [25], however, is clinically unacceptable because of significant side effects in the majority of patients [25].

Based on recent experimental and clinical studies, ketamine would be expected to have no or only minor effects on perception of non-noxious and phasic painful stimuli, such as thermal thresholds, in normal skin of human volunteers. Rather, ketamine is expected to exert its analgesic effects under conditions where tissue damage (e.g. a burn injury) or repetitive C-fibre stimulation has induced hyperexcitability of dorsal horn neurones. This study seems to confirm this assumption. Ketamine in clinically relevant, analgesic doses had no effect on thermal thresholds in undamaged skin, but reduced heat hyperalgesia at the site of injury. In contrast, HPDT in both normal and injured skin was increased after administration of extradural morphine 4 mg [20]. The differential effects of ketamine and morphine on thermal thresholds in normal and hyperalgesic skin are in agreement with the different mechanisms of action (see above).

Primary hyperalgesia is most probably caused by a combination of sensitization of peripheral receptors and central neurones, although the relative contribution of these components is not well established [13]. As ketamine increased HPDT in the primary hyperalgesic area, and as a peripheral effect of ketamine is not anticipated, the results of this study indicate that central sensitization contributes significantly to primary hyperalgesia. We observed further that pain during a prolonged noxious heat stimulus (which resulted in induction of secondary hyperalgesia and hence wind-up and sensitization of dorsal horn neurones), was reduced by ketamine in a dose-dependent manner. In accordance, Park and colleagues [26] reported reduction of ongoing pain evoked by intradermal capsaicin, and Arendt-Nielsen and colleagues [25] reduction of pain evoked by prolonged mechanical stimulation, by ketamine.

We observed that ketamine, in a dose-dependent manner, reduced secondary hyperalgesia for punctuate and stroke stimuli surrounding the burn injury, and secondary hyperalgesia for punctuate stimuli during brief thermal conditioning stimuli. In agreement with a previous study using higher doses of ketamine (bolus 5 mg, followed by infusion of 40 mg h\(^{-1}\)) [26], the reduction of the area of secondary hyperalgesia was only partial: 7–28 % with low-dose ketamine and 25–28 % with high-dose ketamine. Consequently, ketamine in clinically relevant doses should not by itself be expected to completely abolish pain or central sensitization [26, 27].

In experimental studies, NMDA receptor antagonists, including ketamine and dextromethorphan, have been shown to reduce tachyphylaxis and improve the analgesic effect of other analgesics such as morphine and local anaesthetics [28–32]. Data from clinical studies of postoperative pain are not uniform [7, 8]. In one study, the addition of ketamine 0.5 mg kg\(^{-1}\) to caudal bupivacaine provided better analgesia than bupivacaine alone in children undergoing inguinal herniotomy [7]. In another study, combined infusions of morphine and ketamine did not improve postoperative analgesia compared with morphine alone in patients undergoing elective upper abdominal surgery [8].

Side effects of the ketamine dose regimens used in this study were frequent but clinically acceptable in most volunteers. In general, side effects were most pronounced immediately after bolus injections, and substantially declined or disappeared during continuous infusions of both ketamine 0.15 and 0.30 mg kg\(^{-1}\) h\(^{-1}\). Although ketamine in both doses produced drowsiness, HPDT in healthy skin was unaffected by ketamine. Consequently, we do not believe that drowsiness, or other side effects, introduced any significant bias.

In summary, ketamine reduced the magnitude of both primary and secondary hyperalgesia, and pain evoked by prolonged noxious heat stimulation. In contrast, ketamine did not alter phasic heat pain perception in undamaged skin. The analgesic effects of ketamine in the burn injury model can be distinguished from those of local anaesthetics and opioids [19, 20]. Side effects caused by continuous infusion of ketamine 0.15 mg kg\(^{-1}\) h\(^{-1}\) and 0.30 mg kg\(^{-1}\) h\(^{-1}\) were frequent but clinically acceptable in most human volunteers. These data provide a rationale for a systematic evaluation of the analgesic effect of low-dose ketamine in clinical pain states, such as postoperative pain.

Acknowledgement

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References


